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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,051	CAPLAN, MICHAEL J.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/3/06 has been entered.

2. Claims 34-45 are pending and are being acted upon in this Office Action.

3. The incorporation of essential material in the specification by reference to an unpublished U.S. application is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

4. The attempt to incorporate subject matter into this application by reference to 09/141,220 is ineffective because the host document did not identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the document. See In re Seversky, 177 USPQ 144, 146 (CCPA 1973).

5. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

6. Applicant is reminded that upon the incorporation of essential material by reference to 09/141,220, the sequence listing (computer readable form and paper copy of the sequence listing) must be amended and a statement that the content of the substitute copy of the computer readable form is the same as the amended Sequence Listing and do not include new matter as required by 37 CFR 1.821(e), 10821(f), 1.821(g), 1.825(b) or 1.825(d). The specification as filed discloses only polynucleotides of SEQ ID NO: 1-3 encoding peanut allergens Ara h1, Ara h2 and Ara h3, respectively.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a composition comprising dead *E. coli*. expressing at least one peanut allergen encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 2 and 3 for testing whether the allergen expressing *E coli* elicited an immune response (See page 31 of the specification); (2) upon perfecting the incorporation by reference to 09/141,220, and only then being enabling for a composition comprising dead *E coli* expressing at least one modified peanut allergen Ara h1 whose amino acid sequence differs from that of a wild-type peanut allergen such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the modified peanut allergen Ara h1 has one or more amino acid residues essential to the IgE binding in one or more IgE binding epitopes at the specified positions of (the corresponding SEQ ID NO:) have been substituted for alanine or methionine such as the ones shown in bold and underline in Table 4 at page 22 as disclosed in 09/141,220 wherein the modified peanut allergen is encapsulated inside the dead *E coli* and a pharmaceutically acceptable carrier; (3) upon perfecting the incorporation by reference to 09/141,220, and only then being enabling for a composition comprising dead *E coli* expressing at least one modified peanut allergen Ara h2 whose amino acid sequence differs

from that of a wild-type peanut allergen such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the modified peanut allergen Ara h2 has one or more amino acid residues essential to the IgE binding in one or more IgE binding epitopes at the specified positions of (corresponding SEQ ID NO:) have been substituted for alanine or methionine such as the ones shown in bold and underline in Table 5 at page 23 as disclosed in 09/141,220 wherein the modified peanut allergen is encapsulated inside the dead *E coli* and a pharmaceutically acceptable carrier; and (4) upon perfecting the incorporation by reference to 09/141,220, and only then being enabling for a composition comprising dead *E coli* expressing at least one modified peanut allergen Ara h3 whose amino acid sequence differs from that of a wild-type peanut allergen such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the modified peanut allergen Ara h3 has one or more amino acid residues essential to the IgE binding in one or more IgE binding epitopes at the specified positions of (corresponding SEQ ID NO:) have been substituted for alanine or methionine such as the ones shown in bold and underline in Table 6 at page 23 as disclosed in 09/141,220 and wherein the modified peanut allergen is encapsulated inside the dead *E coli* and a pharmaceutically acceptable carrier, **does not** reasonably provide enablement for (1) any pharmaceutical composition comprising dead *E. coli*. comprising any "modified peanut allergen" whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside the dead *E. coli* such as in the cytoplasm or the periplasm of the dead *E coli* and a pharmaceutically acceptable carrier as set forth in claims 34-37 and 40-45; (2) any pharmaceutical composition comprising dead *E. coli*. comprising any "modified peanut allergen" whose amino acid sequence differs from that of a wild-type peanut allergen Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO:3 wherein the sequence of the modified peanut allergen differs from the sequence of said wild-type peanut allergen by *one or more amino acid deletions, substitutions, or additions* within any IgE binding site of the wild-type peanut allergen as set forth in claim 38 and (3) any pharmaceutical composition comprising

dead *E coli* comprising any "modified peanut allergen" wherein the sequence of the modified peanut allergen lacks any *portion* of the wild-type peanut allergen sequence wherein the modified peanut allergens lacks any portion of the wild-type peanut allergen Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO:3 and wherein said portion includes an IgE binding site as set forth in claim 39 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions to peanut in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 34-37 and 40-45 encompass any pharmaceutical composition comprising any dead *E. coli* encapsulated inside the cytoplasm or periplasm of any modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergens Ara h1, Ara h2 and Ara h3 encoded by nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, wherein the modified peanut has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen.

Claim 38 encompasses any pharmaceutical composition comprising any dead *E. coli* encapsulated inside any modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergens Ara h1, Ara h2 and Ara h3 encoded by nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, wherein the sequence of the modified peanut allergen differs from the sequence of the wild-type peanut allergen by any *one or more amino acid deletions, substitutions, or additions* within any IgE binding site of said wild-type peanut allergen Ara h1, Ara h2 or Ara h3.

Claim 39 encompasses any pharmaceutical composition comprising any dead *E. coli* encapsulated inside any modified peanut allergen whose amino acid sequence differs from that of

a wild-type peanut allergens Ara h1, Ara h2 and Ara h3 encoded by nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, wherein the sequence of the modified peanut allergen such as modified Ara h1, Ara h2 and Ara h3 lack any *portion* of the wild-type peanut allergen sequence and wherein said portion includes any IgE binding site.

Enablement is not commensurate in scope with claims as how to make any modified peanut allergen mentioned above encapsulated inside the dead *E. coli* for a pharmaceutical composition for treating or preventing undesirable allergic reactions and anaphylactic allergic reactions to peanut in any subject.

The specification discloses only the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in a subject. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed pharmaceutical composition is to treat and to *prevent* peanut allergy. The specification relies on the incorporated essential material by reference to U.S.S.N 09/141,220 for the specific modified peanut allergen Ara h1, Ara h2 and Ara h3 that have reduced IgE binding while still maintaining antigenicity or immunomodulatory activity, see paragraph bridging pages 20 and 21. However, the incorporation of essential material by reference to U.S.S.N 09/141,220 is improper and has not been perfected.

Until the incorporation of essential material by reference to 09/141,220 has been perfected and only then the specification provides an enabling disclosure for a composition comprising dead *E coli* expressing at least one modified peanut allergen Ara h1 whose amino acid sequence differs from that of a wild-type peanut allergen such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the modified allergen Ara h1 has one or more amino acid residues essential to the IgE binding in one or more IgE binding epitopes at the specified positions of (SEQ ID NO:2 in 09/141,220) such as the ones shown in bold and underline in Table 4 at page 22 as disclosed in 09/141,220 have been substituted for alanine or methionine wherein the modified peanut allergen is encapsulated inside the dead *E coli* and a pharmaceutically acceptable carrier. Likewise, upon perfecting the incorporation by reference to 09/141,220, and only then the specification provides enabling disclosure for a composition comprising dead *E coli* expressing at least one modified peanut allergen Ara h2 whose amino acid sequence differs from that of a wild-type peanut

allergen such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the modified allergen Ara h2 has one or more amino acid residues essential to the IgE binding in one or more IgE binding epitopes at the specified positions of (SEQ ID NO: 4 in 09/141,220) such as the ones shown in bold and underline in Table 5 at page 23 as disclosed in 09/141,220 and a composition comprising dead *E coli* expressing at least one modified peanut allergen Ara h3 whose amino acid sequence differs from that of a wild-type peanut allergen such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the modified allergen Ara h3 has one or more amino acid residues essential to the IgE binding in one or more IgE binding epitopes at the specified positions of (SEQ ID NO: 6 in 09/141,220) such as the ones shown in bold and underline in Table 6 at page 23 of 09/141,220.

The instant specification at page 33 also discloses the level of allergen released varied and was dependent on the expression vector and protein tested. In general, more Ara h2 was released than Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of IgG1 and IgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response".

Even assuming the incorporation of essential material by reference to 09/141,220 has been perfected, the specification does not teach how to make any and all "modified peanut allergen", any and all modified peanut allergen having any one or more amino acid deletions, substitutions, or additions within which IgE binding sites of which wild-type allergen, and any and all modified peanut allergen lacking any portion of the wild-type peanut allergen sequence as broadly as claimed.

There is insufficient guidance as to which amino acids corresponds to which IgE binding site within the full length amino acid sequence in wild-type Ara h1, Ara h2 or Ara h3 whose amino acid sequence is encoded by nucleotides of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO:

3, respectively, to be modified by deletion, substitution for which amino acid, or addition such that the resulting modified peanut allergen has a reduced ability to bind to or cross-linked IgE encapsulated inside the dead *E coli* for the claimed pharmaceutical composition for treating peanut allergy, much less for preventing peanut allergy. Further, there is a lack of guidance as to the structure of the modified peanut allergen without the amino acid sequence, the corresponding nucleic acid sequence. The term "a portion" could be as little as two amino acids. There is insufficient guidance as to the structure of the modified peanut allergen lacking which "portion" of the wild-type peanut allergen Ara h1, Ara h2 or Ara h3 such that the modified allergen has a reduced ability to bind to or cross-link IgE, the corresponding nucleic acid sequences.

As exemplified by the teachings of Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, expressed in dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h2 when mutated, would result in loss of IgE binding, in turn, expressed in dead *E coli* is useful for a composition for treating allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). A protein without the amino acid sequence has no structure, much less function. Further, IgE epitope analysis using peptide fragments is useful when the antigen is recognized by patients' serum sequentially according to its primary sequence. However, IgE mainly recognizes the conformation, but not the primary sequence of the allergen. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h3 when mutated, would result in loss of IgE binding, in turn, expressed in dead *E coli* is useful for a composition for treating allergy. Without the amino acid sequence of the modified peanut allergen and the corresponding the cDNA encoding said modified peanut allergen, one of skilled in the art cannot make the recombinant modified peanut allergen encapsulated inside the dead *E coli* for the claimed pharmaceutical composition, let alone for *preventing* peanut allergy in the absence of in vivo working example demonstrating the modified peanut allergen could prevent any peanut allergy.

Chatel et al, of record, teach various factors such as the nature of the allergen, the genetic background of mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the genetic background of the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al, of record, teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified peanut allergen, it is unpredictable which undisclosed modified peanut allergen reduces IgE binding.

Given the unlimited number of pharmaceutical composition comprising any modified peanut allergen encapsulated inside the dead *E coli* for the claimed pharmaceutical composition, there is in sufficient *in vivo* working examples showing such undisclosed modified allergen

Even if the wild-type peanut allergens are limited to Ara h1, and Ara h2 encoded by SEQ ID NO: 1 and 2, respectively, Kleber-Janke et al (Protein Expression and Purification 19: 419-424, 2000; PTO 892) teach the level of expression of peanut allergens using BL21(DE3) *Escherichia coli* host cells depends on the nature of the peanut allergen. Kleber-Janke et al teach cDNA encoding Ara h1 and Ara h2 subcloned into the expression vector pET-16b (Novagen) that uses the T7 RNA polymerase-responsive promoter resulted in *ineffective* expression of Ara h1 and Ara h2 as well as Ara h6 in conventional BL21(DE3) *Escherichia coli* (see page 419, col. 2, first full paragraph, in particular). The reason for ineffective expression of Ara h1, Ara h2 and Ara h6 in BL21(DE3) was due to high levels of 8-10% of AGG/AGA in peanut allergens Ara h1 and Ara h2 the least use arginine codons AGG/AGA in *E. coli* (see abstract, page 419, col. 2, in particular).

Finally, the specification discloses immunizing mice with heat killed *E. coli* expressing three different recombinant peanut allergens resulted in three different outcomes (see page 34 of instant specification). The instant specification at page 33 also discloses the level of allergen released varied and was dependent on the expression vector and protein tested. In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicant's arguments filed 11/3/06 have been fully considered but are not found persuasive.

At pages 5-6 of the response, Applicant's position is that in arguing that the cited references Ara h1 (Burks et al), Ara h2 (Stanley et al) and house dust mite allergen Der p1 (Fasler et al) do not demonstrate that making modified allergens with reduced IgE binding is so unpredictable. The examiner was wrong to focus on the supposed "failures" while disregarding

the vast number of "success" that are described in those references. The examiner has not taken into account of the nature and amount of experimentation that would actually be required to identify suitable modifications that are not explicitly described in the application or in the prior art. Applicant's position is that in arguing that the immunological properties of the claimed compositions are unpredictable, the examiner points to the examples in the specification (specifically, Examples 3 and 4). Applicant respectfully submits that the examiner does not accurately describe the contents of the examples she cites. As discussed in the specification, microorganisms such as *E. coli* tend to produce Th1-type (i.e., non-allergic) immune reactions in individuals. In contrast, allergens such as the peanut allergens Ara h 1, 2 and 3 tend to produce Th2-type (i.e., allergic) immune reactions. Thl-type immune reactions and Th2-type immune reactions are mutually inhibitory. One aspect of the present invention is the recognition that, by administering allergens in the context of microorganisms such as *E. coli*, it *might be* possible to cause a recipient individual to mount a Thl-type immune reaction to the administered allergen, and therefore to suppress any Th2-type reaction to that allergen (see specification, for example, [0041]). The specification describes the administration of *E. coli* cells that contain the peanut allergens Ara h 1, 2 or 3 to mice. According to the Examples, high levels of IgG2a (indicative of a Th1-type response) were observed for both Ara h 2 and Ara h 3. High levels of IgG1 (indicative of a Th2-type response) were also observed for Ara h 2. Antibody levels were not high enough for Ara h 1 to detect whether Th2-type or Thl-type responses were occurring. Thus, the specification exemplifies initiation of a Thl-type immune reaction to peanut allergens Ara h 2 and Ara h 3 expressed in *E. coli*. It is true that evidence of a Th2-type reaction was also observed for Ara h 2, but that was explained as resulting from released protein which, obviously, would be expected to induce a strong Th2 response. Those of ordinary skill in the art, armed with these teachings, would have recognized that the immunological properties of the inventive compositions are far more predictable than the examiner suggests.

In contrast to applicant's assertion that the examiner has not taken into account of the Wand factors, the factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. Applicants' attention is directed to the explanation above.

As evidence by the teachings of Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that

when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding.

Stanley *et al* (Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). In fact, even the incorporated by reference to USSN 09/141,220 at page 21 lines 6-13 discloses when either alanine or methionine was substituted for each of the amino acid at positions 144, 145, 147-150 within the IgE epitope 9 of Ara h1 shown in SEQ ID NO: 2 reduced IgE binding. In contrast, the substitution of an alanine for arginine at position 152 of Ara h1 shown in SEQ ID NO: 2 resulted in increased IgE binding.

Although the specification discloses how to screen for IgE binding, once made, again such teachings do not provide any guidance to one of ordinary skill with respect to how to make the variants of any and all modified peanut allergens for the claimed pharmaceutical composition.

With regard to the argument that the specification exemplifies initiation of a Thl-type immune reaction to peanut allergens Ara h 2, mice injected with *E. coli* producing Ara h 2

contained relatively high levels of IgG1 (indicative of a Th2-type response) *and* IgG2a (indicative of a Thl-type response), the examiner acknowledges that the success of *treating* allergic response hinges on the production of Th1-type (i.e., non-allergic) immune reactions in individuals. However, given the results of Ara h2 as shown in the specification, at best, the high level of high levels of IgG1 (indicative of a Th2-type response) *and* IgG2a (indicative of a Thl-type response) merely canceling out each other. As stated in the rejection (please see above), one out of three (33% chance) is hardly a success in modulating Th1 immune response for a pharmaceutical composition for treating peanut allergy given the *highly anaphylactic nature* of the peanut allergens, let alone for preventing any peanut allergy as asserted by the disclosure.

Even assuming the explanation that the released protein is the cause and would be expected to induce a strong Th2 response, it is perhaps the nature of the allergen. As evidence by the teachings of Kleber-Janke et al, Kleber-Janke et al (Protein Expression and Purification 19: 419-424, 2000; PTO 892) teach the level of expression of peanut allergens using BL21(DE3) *Escherichia coli* host cells depends on the nature of the peanut allergen. Kleber-Janke et al teach cDNA encoding Ara h1 and Ara h2 subcloned into the expression vector pET-16b (Novagen) that uses the T7 RNA polymerase-responsive promoter resulted in *ineffective* expression of Ara h1, Ara h2 and Ara h6 in conventional BL21(DE3) *Escherichia coli* (see page 419, col. 2, first full paragraph, in particular). The reason for ineffective expression of Ara h1, Ara h2 and Ara h6 in BL21(DE3) was due to high levels of 8-10% of AGG/AGA in peanut allergens Ara h1, Ara h2 and Ara h6 and the least use arginine codons AGG/AGA in *E. coli* (see abstract, page 419, col. 2, in particular).

At pages 6-7 of the response filed 11/3/06, applicant argues that the specification provides enabling disclosure of modified peanut allergens Ara h1, Ara h2 and Ara h3 via incorporation by reference to US Serial No 09/141,220 at page 20, line 29 to page 21, line 1 of the present application. The enclosed 2001 version of the MPEP (Exhibit A) § 608.01 (p) permits an application could incorporate 'essential material by reference to ...pending U.S. pending application (see page 600-79) incorporation by reference to a pending application and the most current version of MPEP (Exhibit B) § 608.01 (p) mentions that "prior to October 21, 2004, Office policy also permitted incorporation by reference to a pending U.S. application." Applicant also noted in the facsimile that if the referenced application has not been published or issued as a patent at the time of allowance then "applicant will be required to amend the disclosure of the

referencing application to include the material incorporated by reference" (referring to page 600-80). In this case, the incorporated '220 application has been abandoned and, as discussed during the interview, Applicant would be willing to amend the specification of this application to include the material incorporated by reference. Finally, Applicant noted that even under the current version of the MPEP, incorporation by reference of an unpublished patent application can be corrected under 37 CFR § 1.57(g). During a follow-up interview that was held on September 11, 2006, the Examiner indicated that the incorporation by reference was indeed proper and that she would reconsider Applicant's arguments in light of this.

In response, applicant has not amended the specification to include the essential material incorporated by reference to US Serial No 09/141,220.

The incorporation of essential material in the specification by reference to US Serial No 09/141,220 at page 20, line 29 to page 21, line 1 of the present application is improper and ineffective because the host document did not identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the document. See In re Seversky, 177 USPQ 144, 146 (CCPA 1973). Until the incorporation of essential material in the specification has been perfected, the specification as filed does not provide an enabling disclosure to any modified peanut allergens encapsulated in dead *E coli* for a pharmaceutical composition.

Even assuming the incorporation of essential material by reference to 09/141,220 has been perfected and other than the specific modified peanut allergens, the specification still does not teach how to make any and all "modified peanut allergen", any and all modified peanut allergen having any one or more amino acid deletions, substitutions, additions within which IgE binding sites of which wild-type peanut allergen, and any and all modified peanut allergen lacking any portion of the wild-type peanut allergen sequence as broadly as claimed given the highly unpredictability of which one or more amino acids substitution, deletion or additions within the IgE epitope of peanut allergens would reduce IgE binding as evidence by the teachings of Burk et al, Stanley et al and Rabjohn et al. Given the unlimited number of modified peanut allergen, the insufficient *in vivo* working examples demonstrating any and all pharmaceutical compositions comprising any modified peanut allergen could treat or prevent any peanut allergy, an undue amount of experimentation would be required to determine how to make and practice the claimed invention.

9. Claims 34-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for (1) any "modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature" such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared to the wild-type peanut allergen wherein the wild-type peanut allergen is an Ara h1, Ara h2, or Ara h3 with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, and wherein the modified peanut allergen encapsulated inside the dead *E coli* for the claimed pharmaceutical composition as set forth in claims 34-37 and 40-45; (2) any "sequence of modified peanut allergen differs from the sequence of the wild-type peanut allergen Ara h1, Ara h2 or Ara h3 by *one or more amino acid deletions, substitutions, or additions* within any IgE binding site" of said the wild-type peanut allergen encapsulated inside the dead E coli for the claimed pharmaceutical composition as set forth in claim 38 and (3) any "sequence of modified peanut allergen that lacks any portion of the wild-type peanut allergen Ara h1, Ara h2 or Ara h3 protein whose amino acid sequence is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO:3 and wherein said portion includes an IgE binding site as set forth in claim 39 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions to peanut in a subject.

Claims 34-37 and 40-45 encompass any pharmaceutical composition comprising any dead *E. coli* encapsulated inside the cytoplasm or periplasm of any modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergens Ara h1, Ara h2 and Ara h3 encoded by nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, wherein the modified peanut has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen.

Claim 38 encompasses any pharmaceutical composition comprising any dead *E. coli* encapsulated inside any modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergens Ara h1, Ara h2 and Ara h3 encoded by nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, wherein the sequence of the modified peanut allergen differs from the sequence of the wild-type peanut allergen by any *one or more*

amino acid deletions, substitutions, or additions within any IgE binding site of said wild-type peanut allergen Ara h1, Ara h2 or Ara h3.

Claim 39 encompasses any pharmaceutical composition comprising any dead *E. coli* encapsulated inside any modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergens Ara h1, Ara h2 and Ara h3 encoded by nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, wherein the sequence of the modified peanut allergen such as modified Ara h1, Ara h2 and Ara h3 lack any *portion* of the wild-type peanut allergen sequence and wherein said portion includes any IgE binding site.

The specification discloses only the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in a subject. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed pharmaceutical composition is to treat and to *prevent* peanut allergy. The instant specification at page 33 also discloses the level of allergen released varied and was dependent on the expression vector and protein tested. In general, more Ara h2 was released than Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of IgG1 and IgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response". The specification relies on the incorporated essential material by reference to U.S.S.N 09/141,220 for the specific modified peanut allergen Ara h1, Ara h2 and Ara h3 that have reduced IgE binding while still maintaining antigenicity or immunomodulatory activity, see paragraph bridging pages 20 and 21. However, the incorporation of essential material by reference to U.S.S.N 09/141,220 is improper and has not been perfected.

Until the incorporation of essential material by reference to 09/141,220 has been perfected and only then the specification provides a written description for the specific modified

peanut allergen Ara h1 such as the ones shown in bold and underline in Table 4 at page 22 as disclosed in 09/141,220, the modified peanut allergen Ara h2 such as the ones shown in bold and underline in Table 5 at page 23 as disclosed in 09/141,220 and the specific modified Ara h3 such as the ones shown in bold and underline in Table 6 at page 23 of 09/141,220.

Even assuming the incorporation of essential material has been perfected, other than the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 encapsulated inside the dead *E coli* for the claimed pharmaceutical composition, there is inadequate written description about the structure associated with function of any and all modified peanut allergen as broadly as claimed. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) The skilled artisan cannot envision the detailed chemical structure of the encompassed "modified peanut allergen" and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid sequence or the corresponding nucleic acid encoding the modified peanut allergen itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Further, the specification has not described which one or more amino acids within which IgE binding sites of Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3 to be deleted, substituted, added or combination thereof that resulted in reduce IgE binding and effective for treating peanut allergy. The term "a portion" in claim 39 could be as little as one amino acid or could be as long as 100 amino acids. The specification does not adequately describe the structure of any such modified peanut allergen that lacks which "portion", including which IgE binding site of the wild-type peanut allergen sequence such as Ara h1, Ara h2 and Ara h3 encoded by SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3 for the claimed pharmaceutical composition. Since the modified peanut allergen encapsulated in the dead *E coli* for the claimed pharmaceutical composition is not adequately described, it follows that the pharmaceutical composition wherein the modified peanut allergen is

located in the cytoplasm or the periplasm of the dead *E coli* are not adequately described. It also follows that the pharmaceutical composition wherein the modified peanut allergen cannot be detected by any antibody binding without disrupting the dead *E coli* is not adequately described.

One of skill in the art would reasonably conclude that three modified peanut allergens Ara h1, Ara h2 and Ara h3 fail to describe the genus for the claimed pharmaceutical composition for treating or preventing peanut allergy. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments filed 11/3/06 have been fully considered but are not found persuasive.

At pages 7-8 of the response, Applicant's position is that the incorporation by reference to USSN 09/141,2201 is proper and the specification does therefore include explicit and extensive description of representative modified Ara h1, 2, and 3 peanut allergens.

In response, applicant has not amended the specification to include the essential material incorporated by reference to US Serial No 09/141,220.

The incorporation of essential material in the specification as filed by reference to US Serial No 09/141,220 at page 20, line 29 to page 21, line 1 is improper and ineffective because the host document did not identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the document. See In re Seversky, 177 USPQ 144, 146 (CCPA 1973). Until the incorporation of essential material in the specification has been perfected, the modified peanut allergens for the claimed pharmaceutical composition as set forth in claims 34-45 are not adequately described.

Even assuming the incorporation of essential material has been perfected, other than the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 encapsulated inside the dead *E coli* for the claimed pharmaceutical composition, there is inadequate written description about the structure associated with function of any and all modified peanut allergen as broadly as claimed. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) The skilled artisan cannot envision the detailed chemical structure of the encompassed "modified peanut allergen" and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid sequence or the corresponding nucleic acid encoding the modified peanut allergen itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Further, the specification has not described which one or more amino acids within which IgE binding sites of Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3 to be deleted, substituted, added or combination thereof that resulted in reduce IgE binding and effective for treating peanut allergy. The term "a portion" in claim 39 could be as little as one amino acid or could be as long as 100 amino acids. The specification does not adequately describe the structure of any such modified peanut allergen that lacks which "portion", including which IgE binding site of the wild-type peanut allergen sequence such as Ara h1, Ara h2 and Ara h3 encoded by SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3 for the claimed pharmaceutical composition. Since the modified peanut allergen encapsulated in the dead *E coli* for the claimed pharmaceutical composition is not adequately described, it follows that the pharmaceutical composition wherein the modified peanut allergen is located in the cytoplasm or the periplasm of the dead *E coli* are not adequately described. It also follows that the pharmaceutical composition wherein the modified peanut allergen cannot be detected by any antibody binding without disrupting the dead *E coli* is not adequately described.

One of skill in the art would reasonably conclude that three modified peanut allergens Ara h1, Ara h2 and Ara h3 fail to describe the genus for the claimed pharmaceutical composition for treating or preventing peanut allergy.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 34-40 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892) and Vrtala et al (Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449).

The WO 99/38978 publication teaches a composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical

to the ones to be incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The claimed invention differs from the teachings of the reference only in that the pharmaceutical composition comprising modified allergen encapsulated in *E coli* wherein the *E coli* is dead instead of alive and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page 1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFNγ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to heat-killed *E coli* as taught by Fenton using the *E coli* that were engineered to express the modified peanut allergen Ara h1, Ara h2 and/or Ara h3 as taught by the WO 99/38978 publication for a pharmaceutical composition to avoid the ethical problems associated with *live* allergy vaccines in patients as taught by Vrtala et al (see page 293, col. 2, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine and that the antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification while avoiding the ethical problems of such *live* allergy vaccines (see page 293, col. 2, in particular). Claim 42 is included in this rejection because it is obvious that IgE binding to modified peanut allergen cannot be detected without disrupting the dead *E coli* with urea since the modified protein has been aggregated to form inclusion bodies that are located in the cytoplasm.

Applicants' arguments filed 11/3/06 have been fully considered but are not found persuasive.

Applicants' position is that that the potent immunological nature of the anaphylactic peanut allergens of the '978 publication would have discouraged one of ordinary skill in the art from attempting to substitute them into the methods of the '799 patent that have only been described for tamer antigens such as isolated microbial antigens and non-anaphylactic allergens (e.g., from animal danders and pollens, see column 9, line 59 to column 10, line 6 of the '799 patent).

In response, the argument with respect to the '779 patent is moot since the '799 patent is no longer available as a reference for the amended claim.

In contrast to applicant's assertion that the potent nature of peanut allergen would have discouraged one of ordinary skill in the art from attempting to express them in *E coli* for a pharmaceutical composition, the modified peanut allergens Ara h1, Ara h2 and Ara h3 that are rendered non-anaphylactic (tamer allergen) as taught by the WO 99/38978 publication would have encouraged one of ordinary skill in the art to substitute the protein in the heat-killed *E coli* as a carrier for a pharmaceutical composition as taught by Fenton et al. The advantage of antigen expressing dead *E coli* is that antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1855, col. 1, Immunization with heat-killed bacteria, page 1857, col. 2, full paragraph, in particular). Further, the WO 99/38978 publication teaches peanut is highly anaphylactic and there remains a need for a safe and efficacious therapy for allergies (see page 2, lines 21-31, in particular). The WO 99/38978 publication teaches modifying IgE epitope by *masking* the IgE epitope or by altering as little as a single amino acid within the IgE binding site of peanut allergens while retaining the ability of the protein to activate T cells is useful to reduce the clinical response to food allergen such as peanut allergen (see abstract, paragraph bridging pages 2 and 3, in particular).

At page 9 of the response filed 11/3/06, applicant argues that the WO 99/38978 publication "teaches expressing anaphylactic modified allergens such as Ara h 1, Ara h 2 and Ara h 3 in *live E. coli*". The '978 publication therefore cannot teach or suggest the presently claimed composition wherein a modified peanut allergen is encapsulated inside.dead *E coli* as amended. Applicant presumes that the teachings of the '799 patent are no longer required. The Examiner is not implying that the combined teachings of the '978 publication and Yeung are sufficient to yield the claimed invention as presumed.

In response, Fenton et al teach the use of dead *E coli* expressing the antigen of interest as a delivery vehicle for a pharmaceutical composition.

In response to applicant's argument that the '978 publication cannot teach or suggest the presently claimed composition wherein a modified peanut allergen is encapsulated inside dead *E coli* as amended, it is noted that the prior to lysis with urea, the modified peanut allergen produced in *E coli* is encapsulated inside the *E coli* as inclusion bodies which located in the

cytoplasm of *E coli*. In fact, the specification at page 31, lines 21-29 discloses the encapsulated allergens in bacteria *E coli* as a delivery vehicle in the claimed invention were produced in the same strain of *E coli* BL21 transformed with the same expression plasmid pET24 and producing the same protein as taught by the WO 99/38978 publication (see WO99/38978 publication page 16, line 22-29, in particular). The WO 99/38978 publication teaches a composition comprising live *E coli* containing therein at least one peanut allergen such as Ara h1, Ara h2 and Ara h3 where the amino acids within each of the binding sites have been substituted such that the modified allergens have reduced IgE binding compared with the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, in particular). The modified peanut allergen taught by the WO 99/38978 publication is located inside the cytoplasm as inclusion bodies of live *E coli*, which is encapsulated inside the *E coli*. It would have been obvious to one of ordinary skill in the art to render the modified peanut allergen producing live *E coli* as taught by the WO 99/38978 publication dead simply by heat treatment as taught by Fenton et al without lysis. The heat treatment would simply stop the live *E coli* from growing and the recombinant modified peanut allergen would still be inside the dead *E coli*. Further, the recitation of dead *E coli* is an obvious variation of the references teachings of the live E coli as taught by the WO 99/38978 publication.

The arguments with respect to Yeung at page 10-11 are moot since the reference has been withdrawn.

12. Claims 34 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Leclerc et al (J Immunology 144(8): 3174-3182, 1990; PTO 892) and Vrtala et al (Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449).

The WO 99/38978 publication teaches a composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular).

The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical to the ones to be incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The invention in claim 41 differs from the teachings of the reference only in that the pharmaceutical composition wherein the modified peanut allergen is located in the periplasm instead of cytoplasm.

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria (see page 3177, col. 1, Figure 3, Table II, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy in patients (see page 293, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to express the modified peanut allergens in *E coli* as taught by the WO 99/38978 publication in the periplasm of *E Coli* and then heat-killed the *E coli* for a pharmaceutical composition as taught by Leclerc et al to avoid the ethical problems associated with live allergy vaccines in patients as taught by Vrtala et al (see page 293, col. 2, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 99/38978 publication teaches the advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest in the periplasm (see page 3177, col. 1, Figure 3, Table II, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification while avoiding the ethical problems of such *live* allergy vaccines (see page 293, col. 2, in particular).

13. Claims 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892) and Vrtala et al (Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449) as applied to claims 34-40 and 42-43 mentioned above and further in view of WO 92/14487 (published September 1992; PTO 892) and US Pat No 6,270,723 (of record, filed Oct 2, 1998; PTO 892).

The combined teachings of the WO 99/38978 publication, Fenton et al and Vrtala et al have been discussed supra.

The claimed invention in claim 44 differs from the teachings of the references only in that the pharmaceutical composition wherein the *E coli* was killed by chemical treatment instead of heat.

The claimed invention in claim 45 differs from the teachings of the references only in that the pharmaceutical composition wherein the *E coli* was killed using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohols instead of heat.

The WO 92/14487 publication teaches a method of safely killing *E coli* bacteria expressing various colonization factor antigens by chemical treatment such as mild or diluted formalin-treated *E coli* for use as a whole cell vaccine (see page7-8, page 19, line 26, in particular). The WO 92/14487 publication teaches the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page 8, lines 7-9, in particular).

The '723 patent teaches various methods of killing bacteria by chemical treatment such as alcohol (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to inactivate bacteria such as *E coli* for pharmaceutical composition (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the heat used for killing any recombinant modified peanut allergen producing live *E. coli* for a pharmaceutical composition given the highly anaphylactic nature of the peanut allergen as taught by the WO 99/38978 publication and Fenton for the chemical treatment such as mild or diluted formalin-treatment as taught by the WO 92/14487 publication or diluted alcohol (see col. 1, line 21, in particular), or diluted bleach (see col. 10, line 39-40, in particular) as taught by the '723 patent instead of heat as taught by Fenton et al to preserve the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as maintaining greater stability of the antigen against degradation in the intestinal milieu as taught by the WO 92/14487 publication (see page 8, lines 7-9, in particular). The '723 patent teaches chemical treatment such as iodine, bleach, ozone, or alcohol can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Applicants' arguments filed 11/3/06 have been fully considered but are not found persuasive.

Applicants' position is that that the '723 patent teaches methods for sterilizing, decontaminating, or disinfecting materials and the advantages of this pressure based method is that it avoids denaturing proteins as compared to heat or chemical treatment and thereby enhances the immunogenicity of the resulting vaccine (see col. 5, lines 30-36). If anything, the '723 patent therefore teaches away from the prior art uses of chemical and heat.

In response to the argument that the '723 patent teaches solely cryobaric method for preparing vaccines is misleading. The '723 patent also teaches various traditional methods for bacterial inactivation or killing such as the use of chemical disinfectants (formaldehyde, glutaraldehyde, alcohols, mercury compounds, quaternary ammonium compounds, halogenated compounds, solvent/detergent systems, or peroxides (see col. 1, back ground of invention, in particular). As evidence by the teachings of WO 99/38978 publication, the use of mild or diluted formalin can safely kill *E coli* bacteria expressing various antigen of interest for use as a whole cell vaccine and the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page7-8, page 19, line 26, page 8, lines 7-9, in particular). It is within the purview of one ordinary skill in the pharmaceutical art to kill recombinant bacteria for a pharmaceutical composition by means of heat as taught by Fenton et al or by chemical means such as mild formalin-killed bacteria for a vaccine as taught by WO 92/14487 publication or mild alcohol or bleach as taught by the '723 patent while preserving the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication. The motivation to kill the modified peanut allergen expressed in live *E coli* for a pharmaceutical composition is obvious given the ethical

problems for using such live bacteria as allergy vaccines in patients as taught by Vrtala et al (see page 293, col. 2, in particular).

The argument with respect to the Evan et al reference is moot since the Evan et al reference is no longer used as a reference.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 34-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-36 and 38-47 of copending Application No. 10/728,323. Although the conflicting claims are not identical, they are not patentably distinct from each other because the *species* of pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence

that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside such as cytoplasm or periplasm of the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of instant application anticipates the *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the wild-type allergen is found in nature in foods, in peanuts, milk, eggs, seafood, nuts, dairy products, fruit, as well as modified peanut allergen is located in the cytoplasm or periplasm of the dead E coli, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 10/728,323.

Thus the issuance of a patent to instant application (species) anticipates the claims of the copending application (genus). The issuance of a patent to copending application 10/728,323 would include the claims of instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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